REMARKS

Interview and Interview Summary

The Applicant thanks Examiner Chong for the courtesy and time provided to the undersigned representative in the personal interview of September 22, 2009, at the Remsen Building in Alexandria, Virginia. The Applicant's representative confirms that, as described in the Interview Summary dated September 25, 2009, the 35 U.S.C. §103(a) rejection of record, proposed claim amendments and ways to overcome rejections were discussed, and no agreement was made as to claim amendments. However, a change should be made in the check boxes for type of interview from "Telephonic" to "Personal."

Amendments to the Claims

Claims 43-44 have been cancelled, claims 19 and 20 have been amended and new claims 45-55 have been added. Upon entry of these amendments claims 14, 19-28, 30 and 33-42, and 45-55 are pending and currently under examination in the application. Support for the amendments can be found in the specification and claims as filed, and at least at page 24, lines 14 to 27 and Fig. 9A – Fig. 9I. No new matter is added.

Background information is summarized for ready reference in the Table, Fig. 1 and Fig. 2, below.

Comparison Table		
	Use of Antisense Oligodeoxynucleotides (aODN)	**RNA Interference (RNAi)**
Nucleic Acid Reagent As Delivered	Oligodeoxynucleotide, preferably chemically modified (e.g., phosphorothioate linkage) to resist degradation	Double Stranded RNA, such as siRNA, shRNA or miRNA
Mechanism of Action	Binding of one aODN molecule to corresponding mRNAsequence provides a DNA-RNA duplex that is a substrate for RNAse H, which cleaves the RNA strand	Binding of the antisense strand activates RISC complex, which then identifies and cleaves the target mRNA sequence. The activated RISC complex can continue to cleave further target mRNA sequences.
Amplification	None, one aODN molecule is required to inactive each mRNA molecule	A few molecules of dsRNA can be sufficient to almost completely abolish the expression of a gene that was homologous to the dsRNA (Hannon et al. 2002, p. 737, of record)
Subcellular Localization of Nucleic Acid After Delivery In a Dendrimer – Nucleic Acid Mixture	**Nucleus** (Yoo & Juliano, 2000, Nucleic Acids Research 28: 4225-4231, of record)	**Perinuclear Cytoplasm** (Rana, U.S. provisional application number 60/430,520, filed on November 26, 2002, Chiu et al., 2004, Chem. Biol, 11: 1165-1175, of record.)

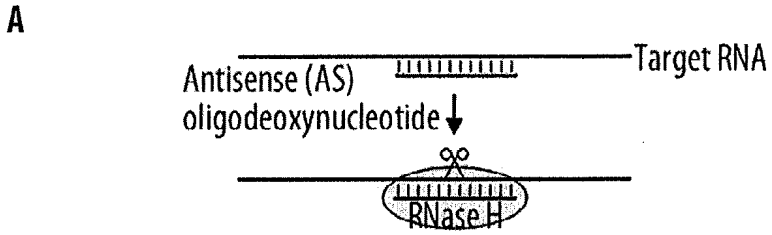

Fig. 1 provides a schematic illustration of the mechanism of the inhibition of gene expression using an antisense oligodeoxynucleotide that hybridizes to the target mRNA, which is then degraded by the intracellular enzyme RNase H that cleaves the RNA strand of the DNA/RNA duplex. Source: Fig.2A of Dallas et al., 2006, Med. Sci. Monit., 12(4): AR67-74, copy submitted herewith.

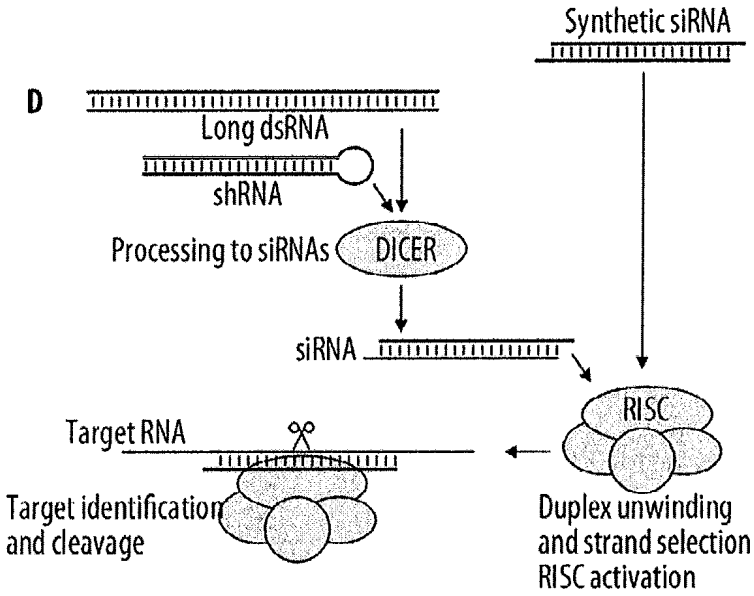

Fig. 2 provides a schematic illustration of the mechanism of the inhibition of gene expression using siRNA. RNA interference uses a multicomponent enzyme complex to degrade target mRNA. Synthetic siRNAs (21-23 bp duplexes) are directly incorporated in the RNAInduced Silencing Complex (RISC). If siRNA precursors are delivered (short hairpin (sh)RNAs or long double-stranded RNAs), they have to be processed by the enzyme Dicer to yield siRNAs. The RISC complex, using AS strand of the siRNA as a guide, searches for the mRNA target and degrades it. that hybridizes to the target mRNA, which is then degraded by the intracellular enzyme RNase H that cleaves the RNA strand of the DNA/RNA duplex. Source: Fig.2D of Dallas et al., 2006, Med. Sci. Monit., 12(4): AR67-74, copy submitted herewith. See also Hammond et al 2001, of record, generally and Fig. 2, and Hannon et al. 2000, of record.

Rejections

The Applicant notes that the rejection of claims 14, 19, 38, 39 and 43 under 35 U.S.C. §102(b) as being anticipated by Szoka et al. (US Patent No. 5,661,025) has been withdrawn.

Rejection under 35 U.S.C. §112, first paragraph, written description

Claim 14 has been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Applicant respectfully traverses this rejection, and requests reconsideration, in view of the amendments to the pending claims and the new claims 45-55.

Rejection under 35 U.S.C. §103(a)

Claims 14, 19-28, 30 and 33-44 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Szoka et al. (US Patent No. 5,661,025 of record cited on PTO Form 892 filed 02/26/2008), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) Olejnik et al. (cited on PTO Form 892 filed 08/23/05) and Grigoriev et al. (cited on PTO Form 892 filed 08/23/05). Claims 43-44 have been cancelled in the present amendment.

A claimed invention is unpatentable due to obviousness if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. §103(a). In order to determine obviousness as a legal matter, four factual inquiries must be made concerning: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) secondary considerations of nonobviousness, which in case law is often said to include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results. *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 57 USPQ2d 1161, 1165 (Fed. Cir. 2000) *citing Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467(1966). The Supreme Court has recently reaffirmed in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (U.S. 2007) that these factors of *Graham v. John Deere Co.* control the analysis of whether claimed subject matter is obvious under 35 U.S.C. §103(a).

A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1395 (U.S. 2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S.

57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). Furthermore, in order to reject a claim based on the rationale that there is some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention, in addition to resolving the *Graham* factual inquiries, the Patent Examiner must articulate the following:

(1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) a finding that there was reasonable expectation of success; and

(3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness (MPEP Rev.6, September 2007 at page 2100-138). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. See MPEP, 2143.02.III, citing *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).

Motivation to Combine References

The Office Action alleges that the Szoka et al. reference teaches DNA, RNA and RNA:DNA hybrid oligonucleotide molecules wherein the molecules are mixed with PAMAM dendrimers having generations 2 to 5 (see columns 9 and 10 and see Table 2), and further teaches the delivery mixture comprising a dendrimer and oligonucleotide is capable of delivering the oligonucleotides molecule to subcellular component of a cell (Office Action, page 6). The Office Action also alleges that the Tuschl et al. reference teaches siRNA molecules, 19-23 nucleotides in length comprising 3' 2 nucleotide overhangs that are effective at mediating RNAi wherein the nucleotides of the sense strand and antisense strand are complementary to the target gene, and that the McManus et al. reference teaches shRNA and microRNA, which are effective at mediating RNAi (Office Action, pages 6-7). The Office Action further alleges that the Olejnik et al. reference teaches oligonucleotides comprising photocleavable biotin and that the Grigoriev et al. reference teaches the incorporation of psoralens into oligonucleotides for formation of psoralen crosslinks (Office Action, page 7). The Office Action concludes that

> One would have been motivated to make a delivery mixture comprising a dendrimer and a siRNA or a microRNA or shRNA because Tuschl et al. and McManus et al. both teach such nucleic acid compounds are more efficient **at silencing gene**

> **expression** and are very useful for determining the function of a gene. (Office Action, page 7, emphasis added).

The alleged motivation to combine references is predicated on substituting the phrase "silencing gene expression" for the plain language of the claim, "effective to mediate RNA interference (RNAi)." "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). The Applicant respectfully submits that the rejection of claims 14, 19-28, 30 and 33-42 under 35 U.S.C. §103(a) as being unpatentable over the combination of the Szoka et al., Tuschl et al., McManus et al., Olejnik et al., and Grigoriev et al. references is improper, and should be withdrawn.

Reasonable Expectation Of Success

The Examiner has made no finding has been made that there would be a reasonable expectation of success. On the contrary, the facts in evidence strongly support a finding that there would be no reasonable expectation of success.

As previously stated in the Amendment and Response filed November 7, 2006, the proposal that one of ordinary skill would substitute siRNA for the antisense oligonucleotides of Yoo et al., is, at best, an "obvious to try" argument. "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d, 943, 945 (Fed Cir. 1990). However, "obvious to try is not the standard," what is required is a "reasonable expectation of success." *In re O'Farrell,* 853 F.2d 894, 904 (Fed. Cir.1988).

The report by Yoo et al. 2000, that a mixture of dendrimer and antisense oligonucleotide delivers the antisense oligonucleotide to the nucleus is consistent with other prior art on other delivery mixtures. A delivery mixture of cationic lipids and antisense oligonucleotide delivers the antisense oligonucleotide to the nucleus (Marcusson, E.G., et al., Phosphorothioate oligodeoxyribonucleotides dissociate from cationic lipids before entering the nucleus, Nucleic Acids Res., 1998, 26(8):2016–2023, copy submitted herewith). A delivery mixture of liposomes and antisense oligonucleotide also delivers the antisense oligonucleotide to the nucleus (Hu, Q., et al., Subcellular trafficking of antisense oligonucleotides and down-regulation of *bcl-2* gene expression in human melanoma cells using a fusogenic liposome delivery system, Nucleic Acids Res., 2002, 30(16):3632-41, copy submitted herewith). In addition, careful reading of the Szoka et al. reference reveals that the dendrimer plus oligonucleotide mixture delivered antisense oligonucleotides to the nucleus (especially Examples 23-28, columns 39-41).

On the other hand, McManus et al., and Hammond et al., both of record, disclose that RNA interference is mediated by the interaction of siRNA with the cytoplasmic RISC complex. Combined with the reports discussed above that a delivery mixture of dendrimer and antisense oligonucleotide delivers the antisense oligonucleotide to the nucleus, it would not be easy to predict whether a delivery mixture of dendrimer and siRNA would be delivered to the nucleus or the cytoplasm, and whether RNA interference would result.

The studies described in U.S. provisional application number 60/430,520, filed on November 26, 2002, (Example 2 (page 19 line 23 to page 20, line 31 and Figs. 1A and 1B), Example 3 (page 21, lines 1-21 and FIG. 2), and Example 8 (page 24, line 29 to page 25, line 14 and FIGS. 9A –9I)) demonstrate the use of a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with an amount of a nucleic acid effective to mediate RNA interference (RNAi). The time of invention of the presently claimed invention thus is constructively no later that the November 26, 2002, the filing date of U.S. provisional application number 60/430,520. To the Applicant's knowledge, this was the first disclosure that a delivery mixture of a dendrimer and siRNA would be delivered to the perinuclear cytoplasm **and** mediate RNA interference.

The Szoka et al. reference neither teaches nor suggests that a mixture of dendrimer plus a nucleic acid effective to mediate RNA interference would deliver the nuclei acid to the perinuclear cytoplasm where it would mediate RNAi, as disclosed in the present application. *See also* Yoo et al., 2000, Nucleic Acids Res., 28(21): 4225-4231, of record, at Abstract, pp. 4229-4230, and Figs 8 and 9.

Subsequently, those who have tried the substitution of siRNA for the antisense oligonucleotides of Yoo et al., as suggested in the Office Action, have *not* demonstrated that success is likely. As discussed in a previous response, Kang, H. et al., of record, have reported that dendrimer-oligonucleotide complexes were moderately effective for delivery of antisense and only poorly effective for the delivery of siRNA. When compared to transfection using LIPOFECTAMINE™ as a positive control, dendrimers were about as effective in producing reduction of gene expression using antisense, but much less effective in producing reduction of gene expression with siRNA. Kang, H. et al., Tat-conjugated PAMAM dendrimers as delivery agents for antisense and siRNA oligonucleotides, Pharm Res. 2005 Dec; 22(12):2099-106. In contrast, as noted above, the present claimed invention is comparable to LIPOFECTAMINE™ in the concentration range of 20-40 μg/ml of dendrimer.

Unexpected Results

As discussed above, the present invention also provides unexpected results, both quantitatively and qualitatively, which are not taught or suggested by the combination of the Hammond, Tuschl and McManus references with the Yoo et al. reference. The present invention discloses that dendrimer

concentrations above 40 μg/ml are less effective in producing cell uptake and RNAi (Figs. 1 and 2 of the present application) and that the localization of the siRNA at higher concentration of dendrimer is different than produced by either LIPOFECTAMINE™ or concentrations of 20-40 μg/ml. In contrast, the Yoo et al. reference alone or in combination with Hammond, Tuschl and McManus references, indicates an increase in effect with increasing concentrations of dendrimer.

Failure of Others

At noted above, failure of others is one of the secondary considerations or indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). As previously stated in the Amendment and Response filed October 31, 2007, with regards when the replacement proposed by the Examiner (i.e., replacement of an antisense oligonucleotide with an siRNA in a delivery mixture comprising a generation 2 to 5 dendrimer) was carried out in the same laboratory as the experiments and results described in Yoo et al., the results using siRNA were not as good as the results demonstrated using antisense. See Kang et al. Furthermore, the failure of Bielinska et al. to demonstrate effective antisense delivery using a generation 5 dendrimer further supports a lack of reasonable expectation of success of use of a generation 5 dendrimer in delivery mixtures. Thus, the failed results of Kang et al. utilizing a delivery mixture comprising a delivery agent consisting of a dendrimer mixed with an siRNA -- and the failed results of Bielinska et al. utilizing a delivery mixture comprising a delivery agent consisting of a generation 5 dendrimer mixed with an antisense nucleic acid -- support a conclusion of non-obviousness of a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with an amount of a nucleic acid effective to mediate RNA interference.

For the reasons discussed above, the Applicant respectfully submits that the rejection of claims 14, 19-28, 30 and 33-42 under 35 U.S.C. §103(a) as being unpatentable over Szoka et al. (US Patent No. 5,661,025), Tuschl et al. and McManus et al., Olejnik et al., and Grigoriev et al. is unwarranted, and should be withdrawn.

Rejection under 35 U.S.C. §103(a)

The rejection of claims 14, 19-28, 30 and 33-44 under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (Clinical Cancer Research 2001 of record), Tuschl et al., and McManus et al., Olejnik et al., and Grigoriev et al., and evidenced by Milhem et al. (International Journal of Pharmaceutics 2000, Vol. 197:239-241 of record) has been maintained. Claims 43-44 have been cancelled in the present amendment. The Tuschl et al., Olejnik et al., and Grigoriev et al., references are discussed in above.

The Office Action at page 11 characterizes the teachings of the Sato et al. reference as follows:

> Sato et al. teach a generation 4 dendrimer, that when mixed with an antisense oligonucleotide, can efficiently deliver said oligonucleotide to cells in vitro and in vivo. There is nothing in the Sato et al. reference that would discourage one of skill in the art away from the use of a generation 4 dendrimer to deliver nucleic acids. Sato et al. teach dendrimers form very stable complexes with negatively charged nucleic acids, are less cytotoxic and are efficient at delivering nucleic acids even in the presence of serum proteins in cells by protecting the nucleic acid from degradation by exonucleases. (Office Action, p.11).

The teachings of the Sato et al. reference were discussed in detail in the response filed May 23, 2008. Sato et al. does not provide evidence of effective delivery of oligonucleotides to cells to confer antisense activity. While the disclosure of Sato et al. provides results of biodistribution studies of injected ^{111}In-oligo-carrier complexes or *in vitro* cell internalization studies of ^{111}In-oligo-carrier complexes, no evidence is provided that oligonucleotides having antisense activity are effectively delivered to cells. This is acknowledged at page 3611, third full paragraph: "(n)either the scintigrams nor the biodistribution data provide explicit evidence of internalization of ^{111}In-oligo into the i.p. tumor cells; however, this condition is strongly suggested from the results of the *in vitro* internalization study."

The Office Action states that "[t]he examiners reliance on Milhem et al. was only evidentiary for-the use of G4 PAMAM dendrimers as efficient drug delivery vehicles . . ." (Office Action, page 12). The Applicant notes that the narrow teaching of Milhem et al. is "[t]he PAMAM G4 dendrimer solution significantly enhanced the solubility of ibuprofen compared to 2% SDS solution" (Milhem et al. Abstract). Ibuprofen has a molecular weight of 206.28; for comparison, a single nucleotide, thymidine has a molecular weight of 242.23 (Merck Index, 14th Edition, 2006, Whitehouse Station, NJ, page 847 and 1615, respectively, copy submitted herewith). The Applicant respectfully submits that Milhem et al. in itself provides minimal evidence, if any, of the efficiency of a G4 PAMAM dendrimer for the delivery of nucleic acids.

As discussed above, there has been no finding that there is a motivation to combine the cited references to arrive at the presently claimed invention. Similarly, there is no evidence of a reasonable expectation of success.

For the reasons discussed above, the Applicant respectfully submits that the rejection of claims claims 14, 19-28, 30 and 33-42 under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (Clinical Cancer Research 2001 of record), Tuschl et al., and McManus et al., Olejnik et al., and Grigoriev et al., and evidenced by Milhem et al. (International Journal of Pharmaceutics 2000, Vol. 197:239-241 of record), is unwarranted and should be withdrawn.

Conclusion

In light of the amendments and the remarks presented herein, the Applicant respectfully submits that all pending claims are in condition for allowance and requests a timely Notice of Allowance to follow in this case. The Applicant requests that the Examiner telephone the undersigned at (508) 860-1472 in the event that a telephone discussion would be helpful in advancing the prosecution of the present case.

A petition for a three-month extension of time and the required fees are submitted herewith. It is believed that no additional fees or extensions of time are required. In the event any fees or credits are due, the undersigned hereby authorizes the fees or credits to be charged to Deposit Account No. 50-1582.

Respectfully submitted,

October 1, 2009

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